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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,029	03/16/2001	Martin C. Barnardo	1181-251	5589

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	15

DATE MAILED: 04/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,029	BARNARDO ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,20 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence compliance* .

DETAILED ACTION

Status of the claims

The amendment and declaration filed January 16, 2003 is acknowledged and has been entered.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See for example, page 10 of the specification.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-17, 20 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 9, lines 2-10 in the specification. The applicant discloses functionally equivalent variants, derivatives or fragments refer to MHC molecules related to or derived from naturally occurring MHC molecules wherein the amino acid sequence of one or more components of said MHC molecules (e.g. the class I heavy chain, class II) has been modified by single or multiple amino acid (e.g. at 1 to 50, e.g. 10 to 30, preferably 1 to 5

bases) substitution, addition and/or deletion but which nonetheless retains functional activity. On page 9, lines 30-37 in the specification. The applicant discloses that the derivatives and variants are closely related to one or more components of the naturally occurring MHC molecules, e.g. are encoded by nucleic acid molecules with more that 70%, preferably more than 80, 90 or 95% sequence identity to naturally occurring sequences or exhibit such sequence identity to the functional portions of these sequences. Further, on page 11, lines 11-21 the applicant discloses the fragments may be derived from naturally occurring molecules or from functionally equivalent variants or derivatives thereof. Preferably the fragments are between 50 and 500 residues, e.g. 100 and 250 residues in length. The applicant does not disclose all recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof. Further, the applicant does not disclose the nucleic acid sequence encoding the variants, which is required. Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere which or plan for obtaining the claimed chemical invention".

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid sequence encoding the variants is required. See *Fiers v. Revel,* 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.,* 18 USPQ2d 1016.

3. Claims 1-17, 20 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant MHC and HLA monomers, known allelic variants and specific peptides, does not reasonably provide enablement for all recombinant MHC and HLA molecules or functionally equivalent recombinant variants, derivatives or fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to a method of detecting the presence of anti-MHC or (HLA claim 2)) antibodies in a sample comprising contacting the sample with one or more

recombinant MHC or HLA molecules or functionally equivalent recombinant variants, derivatives or fragments thereof. Which each bind to a specific MHC antibody or (HLA) antibody, if present in said sample, and detecting the binding or absence of binding of the antibodies to the recombinant molecule, variants, derivatives or fragments thereof. The specification on page 4, lines 31-37 and page 17 discloses recombinant HLA monomers and recombinant MHC monomers. The applicant discloses functionally equivalent variants, derivatives or fragments refer to MHC molecules related to or derived from naturally occurring MHC molecules wherein the amino acid sequence of one or more components of said MHC molecules (e.g. the class I heavy chain, class II) has been modified by single or multiple amino acid (e.g. at 1 to 50, e.g. 10 to 30, preferably 1 to 5 bases) substitution, addition and/or deletion but which nonetheless retains functional activity. On page 9, lines 30-37 in the specification. The applicant discloses that the derivatives and variants are closely related to one or more components of the naturally occurring MHC molecules, e.g. are encoded by nucleic acid molecules with more that 70%, preferably more than 80, 90 or 95% sequence identity to naturally occurring sequences or exhibit such sequence identity to the functional portions of these sequences. Further, on page 11, lines 11-21 the applicant discloses the fragments may be derived from naturally occurring molecules or from functionally equivalent variants or derivatives thereof. Preferably the fragments are between 50 and 500 residues, e.g. 100 and 250 residues in length. The applicant does not disclose all recombinant MHC molecules or functionally equivalent recombinant variants, derivatives or fragments thereof to detect anti MHC or anti HLA antibodies. It is possible the combinations of variants, derivatives

or fragments thereof may lose their functionality and thus would not work to detect the antibodies.

The working examples in the specification are directed to recombinant monomers HLA-A2 and HLA-B8. At best, the detection of the HLA antibodies can be determined only by using recombinant monomers or known allelic variants. There is no guidance in the specification disclosing which derivatives, variants, fragments or combinations thereof, which can be used for the detection of anti-MHC or anti-HLA antibodies. Such is not seen as sufficient to support the breath of the claims and one skilled in the art cannot practice the claimed invention without undue experimentation, because in order to detect the anti-MHC or anti-HLA antibodies one skilled in the art would have to perform experiments to determine which variants, derivatives or fragments did or did not function to bind to the anti-MHC or anti-HLA antibodies.

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 1-17, 20 and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, and 20 are vague and indefinite because of the use of acronyms: i.e. MHC and HLA. Although the terms may have art-recognized meanings, it is unclear if applicant intends to claim the prior art definitions. The terms should be defined in their first instance.

Claims 1, 2, and 20 the recitation "functionally" is vague and indefinite. It is unclear what is the function (i.e. function as an antigen or something else)? Also if the

fragments are structurally identical to recombinant variants or derivatives. How can they be differentiated? See also deficiency found in claim 6.

Claim 2 is vague and indefinite because applicant insinuates that a binding event has occurred, however, there is no recitation of a step in which a binding event has occurred.

Claim 2, the recitation "functionally equivalent variants" is vague and indefinite. There is no definition provided in the specification for this term and id is unclear what applicant intends. See also deficiency in claim 8

Claim 8, line 36 the recitation "a variant" is vague and indefinite. It is unclear what applicant is trying to encompass.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-3, 5, 9-11 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al (US 5,948,627).

Lee et al disclose a method for detection of HLA antibodies. Lee et al disclose adding serum from a patient to microbeads, each microbead presenting HLA antigens. Lee et al disclose incubating the serum and microbeads for sufficient time for anti-HLA

antibodies to bind to the HLA antigens. Lee et al also disclose the addition of a labeled ligand capable of specifically binding with anti-HLA antibodies bound to the HLA antigens and detecting the presence of labeled ligand bound to the HLA antigens.

With respect to recombinant molecule or derivatives or variants as recited in the instant claims, it is well known in the art that cells produce natural derivatives and the claims do not distinguish from naturally occurring derivates or recombinant receptors on cells. Therefore, the claim reads on naturally occurring derivatives and thus Lee et al anticipate the claim.

5. Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Carosella et al (US 6,528,304.

Carosella et al disclose immunoprecitating an K562-HLA-G2 cell (recombinant HLA) with a monoclonal antibody W6/32 (an antibody against MHC Class I heavy chains (anti HLA-A molecule). Carosella et al disclose detecting the monoclonal antibody with a labeled antibody (col 5, line 66 – col 6 line 25).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al in view of Boguslaski et al (US 5,420,016).

See above for teachings of Lee.

Lee et al differ from the instant invention in failing to teach packaging the components into a kit.

Boguslaski et al disclose assembling various system components into a test kit. By assembling these components into test kits, it makes it more convenient and facile for the test operator (col 7, lines 8-11). Therefore, it would have been obvious to one or ordinary skill in the art to package the reagents and components as taught by Lee et al into a kit because Boguslaski et al teaches that by assembling components into test kits, it makes it more convenient and facile for the test operator.

Response to Arguments

Applicant's arguments, filed January 16, 2003 that the combination of Lee et al reference and Baserga et al reference is improper is found persuasive. Therefore, the rejection has been withdrawn.

Regarding the Declaration by Michael Bunce filed on January 16, 2003 is found persuasive. Therefore, the rejection has been withdrawn. Further, the argument is moot in view of the new grounds of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (703) 305-1444. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 305-3399. The fax phone numbers for

the organization where this application or proceeding is assigned are (703)308-4242 for regular communications and (703)3084242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary W. Counts
Examiner
Art Unit 1641
April 7, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
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04/07/03